REMARKS

Claims 1-11 are pending in this application and stand rejected. Claim 10 has been cancelled by this amendment without prejudice or disclaimer. Applicants have amended paragraph [001] of the specification as suggested by the Examiner to capitalize LIVIAL. Applicants respectfully request entry of the above amendments and reconsideration of the claims.

SPECIFICATION

The Examiner has noted that the use of the trademark LIVIAL in the application and has requested that it be capitalized wherever it appears accompanied by the generic terminology. Per the Examiner's request, LIVIAL has been capatilized. Applicants submit that the chemical and trivial name preceeding Livial in line 2 of paragrapg [0001] is sufficient indicia for LIVIAL®.

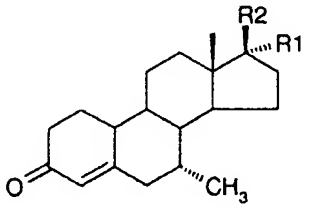
REJECTION UNDER 35 U.S.C §103

Claims 1-9 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Babcock et al (US 3,341,557) and Campbell et al. (Steroids, 1963). Applicants traverse this rejection for the reasons provided herein below.

Claims 1-9 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Babcock et al (US 3,341,557), Campbell et al. (Steroids, 1963) and US 4,400,393. According to the Examiner each of Babcock et al and Campbell et al teaches the production of 7α-methyl derivatives of steroid compounds by reacting the corresponding 4,6-diene-ketone compounds with a methyl Grignard reagent, such as methyl magnesium iodide and methyl magnesium bromide, in the presence of a cuprous salt such as cuprous chloride. The Examiner further asserts that Campbell teaches on page 318, lines 1-4, selectivity and good yield of the 7α-methyl derivatives when the Grignard reagent is utilized in the presence of a cuprous salt. The Examiner asserts that the currently claimed invention differs by the reaction of a trialkylsilyl protected starting material in the process taught by each of Babcock et al and Campbell et al. However, according to the Examiner

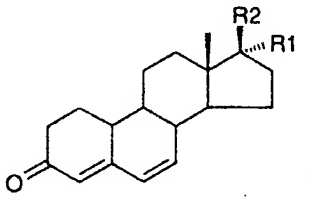
acyl groups and trialkylsilyl groups are known hydroxyl protecting groups (see for example US 4,400,393) Thus, the Examiner asserts the skilled artisan would have a reasonable expectation that the protection of the hydroxyl groups in the compounds taught by Babcock et al and Campbell et al with a trialkylsilyl group instead of an acetyl group would result in the production of the desired 7α-alkylation of the prior art compounds.

Applicants submit that the claimed process is for the preparation of 7α-methyl steroids of the formula I



(I)

wherein R1 is hydrogen, methyl or C≡CH,
R2 is $(CH_2)_nOH$, wherein n is 0, 1 or 2;
by a copper mediated 1,6-conjugate addition of a Grignard reagent CH_3MgX, X being a halogen (Cl, Br or I), to the 4,6-unsaturated 3-ketosteroid of formula II,



(II)

wherein R1 and R2 are as previously defined, comprising protecting the hydroxy group of the steroid of formula II with a trialkylsilyl group, whereby the alkyl group is defined as being a branched or unbranched alkyl group having 1 to 4 carbon atoms, followed by treating the hydroxy protected steroid with the Grignard reagent.

Babcock et al. (US 3,341,557) as well as Campbell et al., (Steroids, 1963), disclose cuprous halide catalyzed 1,6-conjugate addition of methyl magnesium bromide to 17-hydroxyl functional 4,6-unsaturated 3-ketosteroids, whereby the hydroxyl group is

protected with an acetyl group. However, there is no indication in either Babcock or Campbell that the protection of the 17-hydroxyl group is preferred. Furthermore, there is no indication that the protection of the 17-hydroxyl group would result in a better yield of the desired 7α-methyl derivatives.

More particularly, Babcock mentions in column 1, lines 34 to 36, that "in the following formulae, the 7-methyl group represents both the alpha and beta stereoisomers and the mixture thereof." In reaction scheme B, the reaction of compound VIII to compound IX is shown wherein for the substituent –OY the group Y can be selected from hydrogen and an acyl radical. In the paragraph bridging column 4 and column 5 the reaction is described as treating a 6-dehydro-nortestosterone, i.e. a compound with a free hydroxyl group. Again, in column 9, lines 50 to 66, the starting material 6-dehydro-19-nortestosterone (VIII) is mentioned. The preparation of compound VIII is mentioned in column 12, lines 19 to 46, wherein it is specifically said that the 17-acylate groups are deacylated to the free hydroxyl group. Only Example 27 uses acetate as a protecting group but does not mention the yield of the reaction or the amount of the pharmacological interesting 7α-isomers versus the undesirable 7β-isomers.

Campbell discloses in the paragraph bridging pages 317 and 318 that the introduction of a 7α-methyl substituent depends on the observation that 1,6-addition of the methyl Grignard reagent to a Δ4,6-3-ketone can be effected selectively and in good yield in the presence of a cuprous salt to give predominantly the 7α-methyl epimer. In this paragraph, the acetate protecting group is not mentioned. The following literature is cited by Campbell to support its statement: Campbell et al., J. Am. Chem. Soc., 81, 4069 (1959) (copy attached) and Atwater et al., J. Org. Chem., 26, 3077 (1961) (copy attached). Cambell 1959 does not suggest any protecting group in the reaction of 1a to 1b on page 4069. In the paragraph below Chart I it is said that the crude product mainly consisted of 7α, 17α, dimethyl testosterone and a small amount of the 7β-epimer. Atwater suggests a propanoic acid lactone protecting group for the reaction of compound 26 to 27. In the paragraph bridging pages 3078 and 3079 it is said that the α-configuration of the methyl group is based upon the close analogy with the work of Campbell and Babcock

(Cambell 1959). Accordingly, the suggestion made by Campbell in 1963 that the introduction of a 7α-methyl substituent can be effected selectively and in good yield to give predominantly the 7α-methyl epimer is not related to a reaction with a starting material wherein the hydroxyl group is protected by a acetate group.

On page 318, lines 13 to 16, Campbell 1963 mentions that the addition of methyl magnesium bromide in the presence of cuprous chloride under mild conditions afforded 7α-methyl-19-nortestosterone 17-acetate (Vb), accompanied by some of the 17-alcohol. Reference is made to (13) wherein it is said that, alternatively, addition could be effected directly on 6-dehydro-19-nortestosterone if desired.

Accordingly, Babcock and Campbell teach that the use of a free hydroxyl group is equivalent to an acetate group and, thus, provide no indication that a protecting group is required or preferred.

As described above, the presently claimed invention is directed to the stereoselective introduction of the methyl substituent at C-7. The methods published in Babcock et al. and Campbell et al. yield mixtures of the 7α- and 7β-methyl steroids in α,β-ratios ranging from 1.5:1 to 9:1 (page 2, lines 6 to 11 of the specification). Isolation of the pharmacological interesting 7α-isomers from the accompanying 7β-isomers can only be achieved by chromatographic separation or by laborious work-up procedures by repetitive recrystallization. Both operations decrease the yield of the desired 7α-isomer significantly.

In contrast to the methods in Babcock et al and Campbell et al the presently claimed invention provides a process wherein the α,β-ratio is significantly improved by protecting the 17-hydroxyl group of the steroid with a trialkyl silyl group during the reaction. As a result of this protection, surprisingly, a markedly improved stereo-selectivity of the Grignard reaction in favor of the desired 7α-methyl isomer is obtained. More particularly, levels of the unwanted 7β methyl-isomer are decreased to levels below 2.5% (α,β-ratio higher than 39:1). Thus, this claimed process provides for the first time a

straightforward approach for increasing the stereoselectivity of 7α-isomers. Consequently, laborious work-up procedures by troublesome chromatographic separations or by repetitive recrystallization are unnecessary (page 4, lines 5 to 10, of the specification).

US 4,400,393 (US '393) does not teach or suggest that in steroid chemistry wherein 4,6-diene-ketone compounds are reacted with a methyl Grignard reagent a trialkyl silyl group protecting group is preferred and has significant advantages over a free hydroxyl group or an acetate protecting group. More particularly, US '393 relates to bicyclooctane compounds wherein a hydroxyl group can be present either protected or non-protected. US '393 does not provide any teaching on steroids, α- or β-isomers, the desired selectivity for a pharmacological interesting α-isomer, and the way to obtain that.

Furthermore, a side-by-side comparison to prepare 7α-methyl nortestorone from Δ6-nandrolone shows that an unprotected 17-hydroxyl group provides an α,β-ratio of 85:15. According to Campbell, this result is comparable to the use of an acetate protecting group. When the 17-hydroxyl group is protected with a silyl group an α,β-ratio of 95:5 is obtained.

In view of the above, Applicant is of the opinion that a person skilled in the art would not have expected that the replacement of the acetyl group in Babcock et al or Campbell et al by a silyl group would lead to the improved results of stereoselectivity mentioned by Applicant, i.e. an α,β-ratio higher than 39:1 with respect to the desired 7α-methyl isomer. For all of these reasons, Applicants respectfully request withdrawal of the rejection of claims 1-9 over Babcock et al, or Campbell et al and US '393 under 35 U.S.C. §103(a).

Claim 10 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over Peters et al (WO 01/58919). Claim 10 has been cancelled without prejudice or disclaimer. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 11 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over Babcock et al, or Campbell et al and Peters et al (WO 01/58919). Peters et al discloses the 21-acylated hydroxyl-19-norpegn-4,6-dien-3-one (Figure 8, compound 9). The Examiner asserts that, based on the level of the skill of the ordinary artisan in the art, it would have been obvious to modify the process of Babcock and Campbell utilizing any 21-hydroxyl protected derivative of the compound of Peters therein including that of compound 9 of Peters with the reasonable expectation of obtaining the corresponding 7α-methyl derivative.

In response, applicants submit that Peters et al teaches 7α-alkylation using a lower alkyl lithium in the presence of lithium bromide wherein the hydroxyl moiety is protected with a suitable protecting group. This process differs from the process of the current application. Further, a suitable protecting group as in Peters et al includes an alkyl, acetyl, mesylate (Ms), tosylate (Ts), and THP. More specifically, Peters et al teaches that particularly the "use of acetate as the Pr^1 protecting group greatly facilitates the addition of the 7-alkyl group in the α-position." Peters et al reasons that "[w]hile not wishing to be limited by theory, it is believed that the acetate moiety forms a complex with the lithium and promotes introduction of the 7-alkyl functionality from the α-face of the steroid" (Peters et al page 20, lines 23-26). Accordingly, Peters et al teaches the use of an acetate protecting group in a process using alkyl lithium in the presence of lithium bromide to a 7α-alkylated steroid. Considering the difference in 7α-alkylation processes and Peters et al's preference for an acetate protecting group, there is no motivation in Peters et al to modify compound 9 in Figure 8 to prepare the trialkylsilyl protected substrate for the process of the current application.

Therefore, Applicants respectfully request withdrawal of the rejection of claim 11 over Babcock et al, or Campbell et al and Peters et al under 35 U.S.C. §103(a).

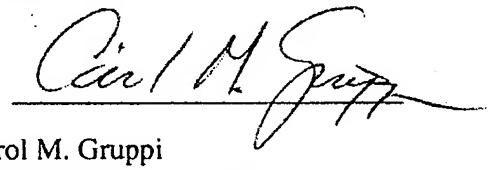
CONCLUSION

In view of the above amendment and remarks, Applicants believes the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

If the undersigned can be of assistance to the Examiner, please contact the undersigned at the number set forth below. In the event the United States Patent and Trademark Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with this filing to Deposit Account No.: 504205. Reference Number: 2002.712 . Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

Dated: May 29, 2009

Respectfully submitted,

By 

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